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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/499,526	02/10/00	LU K	ONV.058.01

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FOLEY, HOAG & ELIOT, LLP
PATENT GROUP
ONE POST OFFICE SQUARE
BOSTON MA 02109

EXAMINER	
DEBERRY,R	
ART UNIT	**PAPER NUMBER**
1647	13

DATE MAILED: 03/12/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/499,526	LU ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-23,28-33,39,42,43,45,46,50 and 51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-23,28-33,39,42,43,45,46,50 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims *13-23,28-33,39,42,43,45,46,50 and 51* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

Status of Application, Amendments and/or Claims

The request for correction of filing receipt received 19 January 2001 has been entered in full (Paper No. 9). The change of address/power of attorney, received 25 January 2001 has been entered in full (Paper No. 12).

Election/Restriction

Applicant's election to prosecute the claims of Group IV (Paper No. 10) with traverse is acknowledged. The traversal is on the grounds that the Examiner has not shown that the second requirement (the search and examination of the entire application cannot be made without serious burden {MPEP 803}), has been met with respect to the Groups. This has been fully considered but is not persuasive. Contrary to Applicants' assertion that the searches required for claims drawn to various PYY-related compounds would substantially overlap and would not require an undue search burden, a search is directed to references which would render the invention obvious, as well as references directed to anticipation of the invention, and therefore requires a search of relevant literature in many different areas of subject matter. A search and examination of all the groups in one patent would result in an undue burden, because the searches for these groups are non-coextensive, the classification is different and/or the subject matter is divergent. The requirement is still deemed proper and is therefore made **FINAL**.

Applicant requested that new claims 51 and 52 in amendment B, received 19 January 2001 (Paper No. 11) be added to Group IV. Claim 51 is drawn to a method of claim 13, wherein administering the PYY Therapeutic causes maturation of said pancreatic islet or cell. Claim 52 is drawn to a method of claim 13, wherein said pancreatic islet or cell is a stem cell. Applicant states that the new claims 51 and 52 depend from claim 13 or Group IV and are properly included within Group IV. This is partly persuasive. Claim 52 will not be added to Group IV because this will result in a different search. Stem cells are not terminally differentiated i.e. not at the end of a pathway of differentiation. They can divide without limit (or at least for the lifetime of the animal). Stem cells, when they do divide; each daughter can either remain a stem cell or it can embark on a course leading irreversibly to terminal differentiation. Pancreatic islets /cells are terminally differentiated. Pancreatic progenitors cells can differentiate into a cell of pancreatic lineage. Stem cells have the potential to differentiate into many different cell lineages (not just pancreatic cells) or not differentiate at all.

Claims 1-12, 24-27, 34-38,40,41,44,47-49,52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Claims 13-23,28-33,39,42,43, 45,46,50 and 51 are under examination. Applicants timely traversed the restriction (election) requirement in Paper No. 10.

Drawings

This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed. If the filed drawings are formal drawings, please indicate as such in response to this Office action and the drawings will be reviewed by the draftsman.

Claim Objections

Claims 30-32,39,42,43,50 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits. Appropriate correction is required.

Claim 29 is objected to because of the following informalities: Claim 29 recites the number 24 twice. Appropriate correction is required.

Claim 15 and 46 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 15 is drawn to the method of claim 14, wherein said glucose responsive islet or cell produces insulin when treated with glucose. Claim 15 does not further limit because there is no mention of islets or cells being treated with glucose. Claim 46 is drawn to the method of claim 45, wherein said pancreatic islet is a failing β cell. Claim 46 does not further limit because normal pancreatic islet function cannot be maintained in a cell or islet that is failing. Applicant is required to cancel the claim(s), or amend the claim(s)

to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Objection to Specification

The disclosure is objected to because of the following informalities: There are two "Example 5" on page 50. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-23,28-33,39,42,43,50 and 51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for stimulating the ability of fetal islets in culture to respond to glucose by secreting insulin by administering PYY and restoring glucose responsiveness in adult rat islets in culture by administering PYY, does not reasonably provide enablement for the following methods claimed: altering the differentiated state of a pancreatic islet/cell comprising administering to a pancreatic islet/cell a PYY Therapeutic (*in vitro* or *in vivo*), modifying glucose metabolism in an animal (or human) or treating a disease associated with altered glucose metabolism comprising administering to an animal (or human) a PYY

Therapeutic and method of obtaining functional pancreatic β cells, comprising administering to a pancreatic islet or cell a composition comprising a PYY Therapeutic. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification has not demonstrated that the differentiation state of the pancreatic islet/cell in culture has changed in response to PYY. While the specification does demonstrate glucose responsiveness in response to PYY in culture, this does not prove differentiation. Genes are selectively expressed and those products act to produce a cell with a specialized phenotype. That differentiated cell does not necessarily produce all of the same proteins all the time, but may respond to stimuli by changing the pattern of expression. Such is not tantamount to "changing the differentiation state" of the cell. The specification does not show where various assays were done to show morphological changes, expression of specific genes or surface markers to demonstrate that differentiation has taken place.

Furthermore, the specification is enabled for PYY but not "PYY Therapeutic" or any biological equivalent, analog, derivative or variant of PYY. The specification does not teach how to make any variant of PYY polypeptides and provides no assay to evaluate the function of any modified polypeptide. In addition, according to the specification, the term "PYY Therapeutic" is not limited to any specific protein (page 9, lines 22-25). Absent any means to assess the function of the polypeptide, it would require an indeterminate quantity of fundamentally unpredictable investigational

experimentation of the skilled artisan to determine whether any modified polypeptide could be used in the same manner as the native exemplar. Such experimentation would be undue for one skilled in this art.

The disclosure provides no guidance as to which regions of the protein would be tolerant of modification and which would not, and it provides no working example of any variant sequence which would be within the claims. It is in no way predictable that randomly selected mutations, deletions, etc. in the disclosed sequence would afford a protein having activity comparable to the one disclosed.

For sequences having one or two substitutions, for example, the artisan would reasonably expect that many of the possible variants would retain functional properties comparable to those of the unmodified protein, and it would require only routine manipulations to make and test a reasonably representative sampling of the possible variants. However, as the number of modified sites increases, the number of possible variants, and hence the degree of experimentation required, increases exponentially. Additionally, as plural substitutions are introduced, their interactions with each other and their effects on the structure and function of the protein become progressively less predictable. The artisan would accordingly have no resort save trial-and-error experimentation to determine which of the astronomically large number of possible structural variants had the functional properties of the claimed proteins. For the reasons discussed above, such experimentation would be undue for one skilled in this art. In this connection, the Board and the Federal Circuit have held in several instances that the disclosure of a single amino acid sequence is not sufficient to enable claims directed

to any functionally equivalent variants of that sequence. See, for example, Ex parte Maizel, 27 USPQ2d 1662 (BPAI 1993).

Lastly, the physiological response of cells in culture does not necessarily or predictably correlate with an effect *in vivo*. The specification is not enabled for the following *in vivo* methods claimed: altering the differentiated state of a pancreatic islet/cell comprising administering to a pancreatic islet/cell a PYY Therapeutic, modifying glucose metabolism in an animal (or human) or treating a disease associated with altered glucose metabolism comprising administering to an animal (or human) a PYY Therapeutic, and obtaining functional pancreatic β cells comprising administering to a pancreatic islet or cell a composition comprising a PYY Therapeutic.

Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teaches that it is recognized in the art that there are many differences between cultured cells and their counterparts in vivo. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light. It is well known in the art that cells in culture exhibit characteristics different from those in vivo and cannot duplicate the complex conditions of the in vivo environment involved in cell-cell interactions. Thus, based on the cell

culture data presented in the specification, it could not be predicted that the same thing would occur in the in vivo environment.

In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The peptide may be inactivated in vivo before producing a sufficient effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half-life of the protein. In addition, the peptide may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the peptide has no effect, circulation into the target area may be insufficient to carry the peptide and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed inventions with a reasonable expectation of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-23,28-33,39,42,43,45,46,50 and 51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "PYY Therapeutic" is indefinite because it is not clear whether it is a compound or composition. The metes and bounds of "PYY Therapeutic" cannot be determined from the claims. The claims do not convey to one skilled in the art the structural and functional requirements of PYY to satisfy the limitations of the claim.

Claims 13-23,28-32,39,42,43,50 and 51 are indefinite. The term "altering the differentiated state" in claims 13-20,30-32,39,42,43,50, and 51 is vague because it is not clear if the term means causing the cell to differentiate, de-differentiate, or if it merely suggests any change in the cells. The term "modifying glucose metabolism" in claims 21,22,30-32,39,42,43 and 50 is vague because it is not clear how glucose metabolism is changed. The word modify is not clear, descriptive scientific language because it encompasses various meanings. The term "pharmaceutically effective amount" in claims 21-23,28-32,39,42,43 and 50 is vague because it is not clear the amount necessary to bring about the desired effect.

Claim 33 is indefinite. Claim 33 provides for the method of obtaining functional pancreatic β cells comprising administering to a pancreatic islet or cell a composition comprising a PYY Therapeutic, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active,

positive steps delimiting how this use is actually practiced. It is unclear how functional pancreatic β cells are obtained.

Claims 13-20,22,30-32,33,39,42,43,45,46,50 and 51 are indefinite because of the interchangeably use of the words "pancreatic islet or cell". While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The term "pancreatic islet" in claims 13-20,22,30-32,33,39,42,43,45,46,50 and 51 is used by the claim to also mean "cell", while the accepted meaning of islet is " a structure containing a cluster of cells in the pancreas that produce insulin " (Dox, I.G. *et al.*)

Claims 28,29,30-32,39,42,43 and 50 are indefinite because they depend on claims drawn to a non-elected group. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claims 13,21,33 and 45 are indefinite because the claims must achieve the goal stated in the preamble. The claims do not have a step that clearly relates back to the preamble.

Claims 15,30,31,42,43, and 50 are indefinite because of the following reasons: Claim 15 recites the limitation "said glucose responsive islet or cell". There is insufficient antecedent basis for this limitation in the claim on page 54. Claims 30 and 31 recite the limitation "said composition". There is insufficient antecedent basis for this limitation in the claims on page 55. Claims 42 and 43 recite the limitation "antagonist".

There is insufficient antecedent basis for this limitation in the claims on page 56. Claim 50 recites the limitation "said animal". There is insufficient antecedent basis for this limitation in the claim on page 57.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on Mondays-Fridays 8:00 a.m. - 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 308-2742 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD
March 8, 2001

LORRAINE SPECTOR
PRIMARY EXAMINER